DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the experimental design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. DO NOT EXCEED THE SPACE PROVIDED.

The killing of microorganisms by phagocytic leukocytes is a major mechanism of defense against bacterial infection in humans. Upon contact with a microorganism, the phagocytic leukocyte undergoes a series of changes that includes activation of a membrane-bound oxidase that catalyzes the reduction of oxygen to superoxide, conversion of superoxide to hydrogen peroxide both spontaneously and through catalysis by the enzyme superoxide dismutase, and formation of hypochlorous acid by the action of myeloperoxidase on hydrogen peroxide and chloride ion. Hypochlorite is an especially effective antimicrobial agent that is also cytotoxic to tissues. However, the mechanism by which hypochlorite kills bacteria and injures tissues has not been fully elucidated. The present proposal is based on the recent discovery by the principal investigator that hypochlorite reacts with adenine nucleotides to form a chlorine-containing free radical product. This product has been isolated and found to oligomerize and form stable ligands with nucleic acids and proteins. In addition, guinea pig polymorphonuclear leukocytes have been shown to incorporate [^{14}C]adenosine into acid-insoluble products in a manner that is dependent upon immunochemical activation of the cells and consistent with the formation of a hypochlorite-modified adenosine intermediate that combines with macromolecular components. The proposed study will further characterize the ability of polymorphonuclear leukocytes to generate nucleotide radicals from labeled precursors and will examine the nature of the adducts that are formed. The method of approach will involve isolation of the labeled products followed by site-specific cleavage by appropriate enzymes and characterization of the radioactive fragments by high-pressure liquid chromatography and electrophoresis. The synthesis of hypochlorite and its reaction with nucleotides is possible whenever excess peroxide is generated, such as during exposure to radiation and certain chemicals, and following periods of ischemia. The formation and linkage of nucleotide radicals to enzymes could result in altered catalytic activity, while linkage to DNA could be carcinogenic. A knowledge of the nature of these radicals and the adducts they form will lead to a better understanding of hypochlorite toxicity and its possible relationship to disease processes associated with the inflammatory response.

KEY PERSONNEL ENGAGED ON PROJECT

NAME, DEGREE(S), SSN	POSITION TITLE AND ROLE IN PROJECT	DEPARTMENT AND ORGANIZATION
Carl Bernofsky, Ph.D. [redacted]	Research Professor, Principal Investigator	Department of Biochemistry Tulane University School of Medicine

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